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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/250,056	02/12/1999	JAMES D. MARKS	2307E-852	1647

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/250,056	MARKS ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,34-44 and 53-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,34-42 and 53-67* is/are rejected.

7)☒ Claim(s) *14,15,43 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/9/04 has been entered.

2. Claims 1, 3-5, 39-40, 53 have been amended, claims 55-67 have been added.

3. Claims 1, 3-15, 34-44, 53-67 are pending and under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Claim Objections

6. Claims 4, 63 are objected to because of the following informalities: the claims have the phrase "<<<page32, lines 5-9>>>" in claim 4 and "<<<page 28, lines" in claim 63. The phrases appear to be where support is found in the specification.

Appropriate correction is required.

Rejections Withdrawn

7. The rejection of claims 34-38, 43-44, 53-54, under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1, 34-38, 53-54 under 35 U.S.C. 103(a) as being unpatentable over Maier et al (Cancer Res 51:5361-5369, 1991) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is withdrawn in view of the declaration of Dr. Kirpotin.

Response to Arguments

9. The rejection of claims 3-13, 39-42, and 61-63, under 35 U.S.C. 112, first paragraph, is maintained and made again.

The response filed 8/9/04 did not address this rejection. As such the rejection is maintained. The rejection is maintained because the claims encompass antibodies with less than a full set of CDRs from SEQ ID NO:1 and 2 and conservative substitutions in the CDRs as well as frameworks and CDRs with 70% sequence to the CDRs of SEQ ID NO:1 and 2. Claim 61 encompasses antibodies with the VH or VL of SEQ ID NO:1 or 2 replaced with a human VH or VL and again it is unpredictable which if any human VH or VL would be able to pair with the VH or VL of SEQ ID NO:1 or 2 and produce a binding antibody as well as internalize. Thus the prior art teaches that antibodies that do not have a full set of CDRs from the light and the heavy chain of a specific antibody do not bind antigen as evidenced from Rudikoff, Amit, and Panka. The prior art addresses antibodies as defined by the claims which would not bind antigen. The prior art teaches

that it is unpredictable which CDRs and frameworks (one or two in each chain as defined by the claims) to only substitute or which residues to maintain to obtain the required binding. The specification has not taught how to make antibodies as broadly defined by the claims that bind c-erbB2 and internalize. As evidenced from Colman (Research in Immunology 145:33-36, 1994) even very conservative substitutions can abolish the binding of an antibody (see page 35). Thus, even conservative substitutions are unpredictable as far as obtaining antigen binding antibodies are concerned. Therefore, it would require undue experimentation to produce the claimed invention.

10. The rejection of claims 1, 34-38, 53-54 and newly added claims 55-57, 59-60, 67 under 35 U.S.C. 103(a) as being unpatentable over Xu et al (int. J. Cancer 53:401-8, 1993) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is maintained.

Claims 55-57 and 59-60, 67 are included in this rejection and recite affinity of 10^{-5}M, single chain, homodimer, and the binding of the antibody is reduced in the presence of F5 or C1 and the antibody is prepared chemically or expressed from a cell. For this rejection the product by process limitation has been met. The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior

product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

The response filed 8/9/04 has been carefully considered but is deemed not to be persuasive. The response states that the declaration filed 4/30/04 supports Applicants previous assertion that the epitopes bound by F5 and C1 are not the same as those of Xu. In response to this argument, the declaration of Dr. Kirpotin has been carefully considered as stated in the advisory action mailed 6/8/04 but is reiterated or expanded here. The declaration states that TA1 and ID5 are internalized at 30 and 27% after one hour and they are not internalized as rapidly as C1 or F5 and because of this they do not bind the same epitope as C1 or F5 (see page 4 of declaration). In response to this it is unclear whether given 5-6 hours as in the declaration the antibodies of Xu would be 70-80% internalized as those of the C1 or F5. Therefore, it is still not clear if there is a difference in the binding between the Xu antibodies and C1 or F5.

11. The rejection of claims 1, 34-38, 53-54 and newly added claims 55-57, 59-60, 67 under 35 U.S.C. 103(a) as being unpatentable over Shawver et al (Cancer Res 54:1367-1373, 1994) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is maintained.

Claims 55-57 and 59-60, 67 are included in this rejection and recite affinity of 10^{-5}M, single chain, homodimer, and the binding of the antibody is reduced in the presence of F5 or C1 and the antibody is prepared chemically or expressed from a cell. For this rejection the product by process limitation has been met. The method in which the

antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

The response filed 8/9/04 has been carefully considered but is deemed not to be persuasive. The response states that the declaration filed 4/30/04 supports Applicants previous assertion that the epitopes bound by F5 and C1 are not the same as those of Shawver et al. In response to this argument, the declaration of Dr. Kirpotin has been carefully considered as stated in the advisory action mailed 6/8/04 but is reiterated or expanded here. The declaration states that the antibodies of Shawver et al had a rate of internalization of 28% after 3 hours and they are not internalized as rapidly as C1 or F5 and because of this they do not bind the same epitope as C1 or F5 (see page 4 of declaration). In response to this it is unclear whether given 5-6 hours as in the declaration the antibodies of Shawver would be 70-80% internalized as those of the C1 or F5. Therefore, it is still not clear if there is a difference in the binding between the Shawver antibodies and C1 or F5.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 1, 3-13, 39-42, 55, 67 are rejected under 35 U.S.C. ' 101 because the claimed invention is directed to non-statutory subject matter.

The claims as written, do not sufficiently distinguish over antibodies as they exists naturally because claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and binding compositions and the structure of naturally occurring antibodies. The antibodies were produced from a phage library of blood cells and the heavy and light chains would be in a human.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

Claim Rejections - 35 USC § 103

14. Claims 1, 34-38, 53-54 and newly added claims 55-60, 62, 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shawver et al (Cancer Res 54:1367-1373, 1994) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) and Schier et al (JMB 255:28-43, 1996, IDS).

The claims are summarized as an antibody that binds to the same epitope as F5 or C1 and is internalized and has an effector, and a composition and a single chain antibody, and is on a phage and is produced by chemical synthesis or nucleic acid expression and is from a mutant library in which a CDR is mutated and the binding of the antibody is reduced in the presence of F5 or C1 and the antibody is prepared chemically or expressed from a cell. For this rejection the product by process limitation has been met. The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Shawver et al teach hybridomas and antibodies produced from such that are internalizing and bind to c-erbB2 and labeled antibodies. Shawver et al does not teach a single chain or an immunotoxin or produced on a phage or mutations in the CDRs.

Theses deficiencies are made up for in the teachings of Bird et al and Chaudhary et al and Schier et al.

Bird teach single chain antibodies.

Chaudhary teach single chain immunotoxins.

Schier et al teach affinity driven selection in phage.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Shawver et al and produce a single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Shawver et al and produce a single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection because Bird et al teach "Single chain antigen binding proteins are expected to have advantages in clinical applications because of their small size" (see page 426) and because Chaudhary et al teach the method is rapid and one can obtain the VH and VL genes from PCR and the immunotoxins can be used directly as fusion proteins and domain I of PE promotes internalization (see page 1069). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Shawver et al and produce a single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection because Shawver et al teach radiolabled conjugates of the antibody. In addition it

would have been obvious to use phage to select antibodies because Schier et al teach that scFv can be obtained with affinities comparable to murine antibodies without immunization.

It is the Examiner's position that Shawver et al have produced an antibody that has the same properties as claimed which are binding to the same epitope as F5 or C1 and is internalized recited in the claims. One of ordinary skill in the art would reasonably conclude that Shawver et al's antibody also possesses the same properties as claimed and, therefore, it appears that Shawver et al have produced an antibody that is identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Shawver et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1, 34-38, 53-54 and newly added claims 55-60, 62, 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al (int. J. Cancer 53:401-8, 1993) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) and Schier et al (JMB 255:28-43, 1996, IDS)

The claims have been described supra. For this rejection the product by process limitation has been met. The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Xu et al teach hybridomas and antibodies produced from such that are internalizing and bind to c-erbB2. Xu et al does not teach a single chain or an immunotoxin. Theses deficiencies are made up for in the teachings of Bird et al and Chaudhary et al.

Bird teach single chain antibodies.

Chaudhary teach single chain immunotoxins.

Schier et al teach affinity driven selection in phage.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Xu et al and produce a single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Xu et al and produce a

single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection because Bird et al teach "Single chain antigen binding proteins are expected to have advantages in clinical applications because of their small size" (see page 426) and because Chaudhary et al teach the method is rapid and one can obtain the VH and VL genes from PCR and the immunotoxins can be used directly as fusion proteins and domain I of PE promotes internalization (see page 1069). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Xu et al and produce a single chain or a single chain immunotoxin as taught by Bird et al and Chaudhary et al and use phage display for affinity selection because Xu et al teach ricin A conjugates (which are immunotoxin conjugates) can exert different levels of cytotoxicity (see page 407). In addition it would have been obvious to use phage to select antibodies because Schier et al teach that scFv can be obtained with affinities comparable to murine antibodies without immunization.

It is the Examiner's position that Xu et al have produced an antibody that has the same properties as claimed which are binding to the same epitope as F5 or C1 and is internalized recited in the claims. One of ordinary skill in the art would reasonably conclude that Xu et al's antibody also possesses the same properties as claimed and, therefore, it appears that Xu et al have produced an antibody that is identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Xu et al, the burden of proof is upon the Applicants to show an unobvious distinction between the

structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Summary

16. No claims are allowed. Claims 14-15, 43-44 are objected to as depending on a rejected claim.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER